

RESEARCH ARTICLE

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Population mixing for leukaemia, lymphoma and CNS tumours in teenagers and young adults in England, 1996–2005

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Abstract

Background: Little aetiological epidemiological research has been undertaken for major cancers occurring in teenagers and young adults (TYA). Population mixing, as a possible proxy for infectious exposure, has been well researched for childhood malignancies. We aimed to investigate effects of population mixing in this older age group using an English national cancer dataset.

Methods: Cases of leukaemia, lymphoma and central nervous system (CNS) tumours amongst 15–24 year olds in England (diagnosed 1996–2005) were included in the study. Data were obtained by ward of diagnosis and linked to 1991 census variables including population mixing (Shannon index); data on person-weighted population density and deprivation (Townsend score) were also used and considered as explanatory variables. Associations between TYA cancer incidence and census variables were investigated using negative binomial regression, and results presented as incidence rate ratios (IRR) with 95% confidence intervals (CI).

Results: A total of 6251 cases of leukaemia (21%), lymphoma (49%) and CNS tumours (30%) were analysed. Higher levels of population mixing were associated with a significant decrease in the incidence of CNS tumours (IRR = 0.83, 95% CI = 0.75–0.91), accounted for by astrocytomas and ‘other CNS tumours’; however, there was no association with leukaemia or lymphoma. Incidence of CNS tumours and lymphoma was 3% lower in more deprived areas (IRR = 0.97, 95% CI = 0.96–0.99 and IRR = 0.97, 95% CI = 0.96–0.98 respectively). Population density was not associated with the incidence of leukaemia, lymphoma or CNS tumours.

Conclusions: Our results suggest a possible role for environmental risk factors with population correlates in the aetiology of CNS tumours amongst TYAs. Unlike studies of childhood cancer, associations between population mixing and the incidence of leukaemia and lymphoma were not observed.

Keywords: Population mixing, Aetiology, Teenage and young adult, Adolescent, Oncology, Leukaemia, Lymphoma, Central nervous system tumours

Background

A number of epidemiological studies have reported associations between childhood leukaemia and population mixing [1–4], suggesting a role for infections in disease aetiology. This association is based upon the premise that areas with high levels of population mixing are likely to exhibit higher prevalence and a greater range of

infections [5]. Increased levels of population mixing can be considered as a risk factor for cancer through exposure to some unknown infectious agent(s) as proposed by Kinlen [1]. Alternatively, Greaves [4] proposes a ‘delayed infection hypothesis’ in which increased levels of population mixing provides a protective role through its development of the immune system. This hypothesis is supported by several previous studies of childhood ALL [3,6]. The evidence of a possible infectious aetiology for childhood tumours is most established for childhood leukaemia and lymphoma [2,7–12], but is also emerging

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for central nervous system (CNS) tumours [13-17] although inconsistencies in the research exist for the latter group [18-20]. Despite increasing evidence of an infectious aetiology for childhood tumours, little aetiological research has been undertaken for major cancers occurring in teenagers and young adults (TYA). Indeed, there is a paucity of epidemiological research investigating causal factors for cancer amongst TYAs [21], a population which presents with distinct forms of cancer [21,22].

There is some evidence showing geographical variation in the incidence of TYA cancer, including an inverse association between levels of deprivation and the occurrence of leukaemia, lymphoma and central nervous system (CNS) tumours [23]. We have previously shown evidence of seasonality around the time of diagnosis for Hodgkin's lymphoma and 'other' CNS tumours (subgroup 3.5 - [24]) as well as seasonality around the time of birth for those with glioma (except astrocytoma and ependymoma) [25]. In this study we investigated whether there was any evidence of an association between population mixing and these tumours occurring in 15-24 year olds using the same national dataset in England and an ecological study design. Population mixing is likely to reflect the level of circulating infections within small geographical areas, which are known to be dependent upon population density [26]. We therefore investigated the impact of adjusting for population density and deprivation on the reported association with population mixing, as both covariates were likely to be confounding factors, and possibly correlated.

Methods

Cases of leukaemia, lymphoma and central nervous system (CNS) tumours amongst 15-24 year olds diagnosed between 1996 and 2005 in England were obtained from the national TYA database held by the North West Cancer Intelligence Service (Research Ethics Committee approval 09/H1302/37). All diagnoses were coded according to the Birch classification of cancer for TYA [24]. Age and sex-specific population figures by year and 2001 standard table census ward were obtained from the Office for National Statistics.

For each individual, the full address (including postcode) at diagnosis was geo-coded to census wards. We chose to allocate measures of population mixing, population density and deprivation to each subject based on the 1991 census. This census period overlapped with the modal exposure time for individuals included in the study and so reflected the average level of mixing attributed to the cohort diagnosed from 1996-2005, given the potential exposure time window ranged from 1971-2005. All age population mixing was measured using the Shannon Index [27] as an indicator of the diversity of incoming migrants into each ward during the year before the census, and was derived using 1991 Census Special Migration

Statistics [28]. Ward level population density was person-weighted according to enumeration district to gain a more accurate measure of the average density at which most individuals live [29]. Area based deprivation levels were measured using the Townsend deprivation score calculated from levels of unemployment, household overcrowding, housing tenure and car ownership [30]. These methods are described in detail in a previous ecological analysis carried out in Yorkshire [6].

Statistical methods

Possible associations with leukaemia, lymphoma and CNS tumour incidence and population mixing, population density, and deprivation were initially investigated using Poisson regression. Negative binomial regression was used in cases where data showed evidence of over dispersion by performing likelihood ratio tests of the scale parameter. Due to the possibility of multicollinearity occurring between population mixing, deprivation and population density, correlation between variables was assessed using Spearman's rank coefficient. Likelihood ratio testing and Akaike's Information Criterion (AIC) were used to determine which variables should be included in the models alongside population mixing (the base model) and whether these should be included as continuous or categorical variables [31]. We were also interested in possible threshold effects, and so additionally report categorisation of population mixing into the 1st, 2nd to 9th and 10th deciles, similar to previous analyses [6,32].

Results

There were a total of 6251 cases of leukaemia, lymphoma and CNS tumours diagnosed amongst 15-24 year olds between 1996 and 2005 in England. Table 1 gives the number of cases and incidence rates of leukaemia, lymphoma and CNS tumours according to diagnostic subgroup.

Population mixing was significantly correlated with population density (Spearman's rank coefficient = 0.23, $P < 0.001$), but not with deprivation score (Spearman's rank coefficient = 0.01, $P = 0.396$). There was significant evidence that the data for leukaemia, lymphoma and CNS tumours were over dispersed (likelihood ratio test for the scale parameter being equal to zero gave $P = 0.013$, $P = 0.005$ and $P < 0.001$ respectively). Negative binomial regression models were therefore fitted in favour of Poisson regression models. Incidence rate ratios (IRRs) obtained via negative binomial regression models for population mixing, deprivation scores and population density by diagnostic group are given in Table 2, and for population mixing and deprivation by diagnostic subgroup in Table 3. Model comparisons showed that for all diagnostic groups the best fitting model was obtained by including population mixing and deprivation in their continuous forms, except for leukaemia in which the inclusion of deprivation

Table 1 Leukaemia, lymphoma and CNS tumours amongst teenagers and young adults in England, 1996-2005

Diagnostic group ^a	Cases (subgroup%)	Incidence rate (per 10 ⁶ person-years)
Leukaemia		
Acute lymphoid leukaemia (ALL)	591 (45%)	9.7
Acute myeloid leukaemia (AML)	463 (36%)	7.6
Chronic Myeloid leukaemia (CML)	147 (11%)	2.4
Other leukaemia	98 (8%)	1.6
All leukaemias	1299	21.3
Lymphoma		
Non-Hodgkin's lymphoma (NHL)	991 (32%)	16.3
Hodgkin's lymphoma (HL)	2079 (68%)	34.1
All lymphomas	3070	50.3
CNS tumours		
Astrocytoma	629 (33%)	10.3
Other Glioma	195 (10%)	3.2
Ependymoma	99 (5%)	1.6
Medulloblastoma	111 (6%)	1.8
Other Specified CNS	702 (37%)	11.5
Unspecified CNS	146 (8%)	2.4
All CNS tumours	1882	30.9
All leukaemia, lymphoma and CNS tumours	6251	102.5

^aDefined according to the Birch Teenage and Young Adult Classification Scheme [24].

Abbreviation: CNS central nervous system.

score did not improve the model fit (Table 4). Person-weighted population density did not improve the model fit for any diagnostic group.

For the best fitting models, population mixing did not significantly affect the incidence of leukaemia or lymphoma. However, increased levels of population mixing were associated with a significant decrease of 17% in incidence of CNS tumours for each unit increase in the Shannon index (IRR = 0.83, 95% CI = 0.75-0.91); this is equivalent to an overall incidence rate of 40.5 per million person-years for wards in the lowest centile of population mixing, compared to 26.8 per million person-years in the highest centile of population mixing. The effect of population mixing amongst CNS tumours was driven by astrocytoma (IRR = 0.83, 95% CI = 0.71-0.98) and 'other CNS tumour' subgroups (IRR = 0.79, 95% CI = 0.68-0.92).

Levels of deprivation were not associated with the incidence of leukaemia, however, there was a significant 3% decrease in incidence of lymphoma associated with more deprived areas (IRR = 0.97, 95% CI = 0.96-0.98), which was consistently observed for Non-Hodgkin's and Hodgkin's lymphoma (Table 3). Furthermore, a significant 3% decrease in incidence of CNS tumours was associated with increased deprivation (IRR = 0.97, 95% CI = 0.96-0.99). This effect was also observed within the 'other glioma' (IRR = 0.96, 95% CI = 0.92-1.00) and 'other CNS tumour' (IRR = 0.97, 95% CI = 0.95-0.99) subgroups (Table 3).

Discussion

In the first major study investigating the association between population mixing and TYA cancer, we have shown that higher levels of mixing are significantly associated

Table 2 Incidence rate ratios (IRR) and 95% confidence intervals (CI) for leukaemia, lymphoma and CNS tumours in teenagers and young adults, 1996-2005

Model ^a	Variables	Leukaemia			Lymphoma			CNS Tumours ^b		
		IRR	95% CI	P-value	IRR	95% CI	P-value	IRR	95% CI	P-value
A	Population Mixing	0.92	0.83-1.03	0.144	0.94	0.87-1.01	0.086	0.81	0.74-0.89	<0.001
B	Population Mixing	0.93	0.83-1.04	0.222	0.97	0.90-1.04	0.426	0.83	0.75-0.91	<0.001
	Deprivation Score	0.99	0.98-1.00	0.114	0.97	0.96-0.98	<0.001	0.97	0.96-0.99	<0.001
C	Population Mixing	0.95	0.84-1.07	0.446	0.97	0.90-1.06	0.529	0.82	0.74-0.91	<0.001
	Deprivation Score	0.99	0.98-1.01	0.609	0.97	0.96-0.98	<0.001	0.97	0.95-0.99	0.001
	Population Density ^c	1.00	0.99-1.00	0.433	1.00	1.00-1.00	0.820	1.00	0.99-1.00	0.675
D	Population Mixing									
	1st Decile	0.93	0.73-1.19	0.572	0.97	0.83-1.14	0.689	1.35	1.13-1.61	0.001
	2-9 th Decile	1	-	-	1	-	-	1	-	-
	10 th Decile	0.9	0.77-1.05	0.168	0.98	0.89-1.09	0.718	0.93	0.81-1.06	0.267
	Test for Trend			0.203			0.778			0.075
	Deprivation Score	0.99	0.98-0.99	0.163	0.97	0.96-0.98	<0.001	0.97	0.96-0.98	<0.001

^aBest fitting model is highlighted in bold for each diagnostic group, model fit statistics are given in Table 4.

^bAnalysis for main CNS tumour subgroups are shown in Table 3.

^cPerson-weighted population density.

Table 3 Incidence rate ratios (IRR) and 95% confidence intervals (CI) for main subgroups of leukaemia, lymphoma and CNS tumours in teenagers and young adults, 1996-2005

Diagnostic subgroup	Multivariable model variables					
	Population mixing			Deprivation score		
	IRR	95% CI	P	IRR	95% CI	P
Leukaemia						
Acute lymphoid leukaemia	0.96	0.82-1.13	0.658	0.99	0.97-1.01	0.149
Acute myeloid leukaemia	0.88	0.73-1.06	0.168	0.99	0.97-1.01	0.474
Chronic myeloid leukaemia	0.97	0.71-1.34	0.862	1.01	0.98-1.05	0.497
Other leukaemia	0.89	0.59-1.34	0.575	0.95	0.91-1.00	0.074
Lymphoma						
Non-Hodgkin lymphoma	1.02	0.90-1.16	0.710	0.98	0.97-1.00	0.038
Hodgkin lymphoma	0.94	0.86-1.03	0.204	0.96	0.95-0.97	<0.001
CNS Tumours						
Astrocytoma	0.83	0.71-0.98	0.025	0.98	0.96-1.00	0.069
Other Glioma	0.77	0.57-1.03	0.076	0.96	0.92-0.99	0.026
Ependymoma	0.97	0.65-1.44	0.863	0.96	0.91-1.01	0.092
Medulloblastoma	1.10	0.75-1.60	0.625	0.96	0.92-1.01	0.107
Other CNS tumours ^a	0.79	0.69-0.91	0.001	0.97	0.95-0.99	<0.001

^aIncludes groups 3.5 and 3.6. from Birch Classification Scheme [24].

with decreased incidence of CNS tumours amongst TYAs in England. The incidence of CNS tumours in wards with the highest levels of population mixing was 1.5 times higher compared to the incidence of CNS tumours in wards with the lowest levels of population mixing. A similar magnitude of effect was observed amongst the astrocytoma and 'other CNS tumour' subgroups. Population mixing levels were not significantly associated with the incidence of ependymoma, medulloblastoma and other glioma subgroups, although this is not surprising given that these are much smaller subgroups (5%, 6% and 10% of

total CNS tumours respectively). Population mixing and deprivation did not appear to affect incidence of leukaemia in TYAs, contrasting to evidence of a significant association between both covariates and the incidence of leukaemia in children [6,11]. Similarly, in our previous work focusing on seasonality of birth and diagnosis, our results of TYAs with leukaemia contrasted to those for children with leukaemia [25]. These differences are likely to occur due to differences in the disease epidemiology of leukaemia between these two age groups, whereby ALL dominates childhood leukaemia in contrast to AML more commonly seen in TYAs and the ratio of T-cell to B-cell ALL is higher amongst TYAs compared to children [33-35]; thus suggesting that the aetiology of leukaemia amongst TYAs is very different to that of leukaemia amongst children.

Significantly decreased incidence rates for Hodgkin's and non-Hodgkin's lymphoma, CNS tumours overall, 'other gliomas' and 'other CNS tumours' were associated with more deprived areas. This is consistent with Alston [23] who showed that increased levels of deprivation were associated with decreased incidence of lymphoma and CNS tumours amongst 13-24 year olds in England diagnosed between 1979-2001.

Person-weighted population density did not have a significant effect on the incidence of any of the main cancer groups studied. This could be explained as population mixing was significantly correlated with population density. Future aetiological work should therefore focus on disentangling the confounding effects of population mixing and population density.

Table 4 Comparison of models shown in Table 2

Models	Likelihood ratio test <i>P</i> -value	AIC		Model choice
		Model 1	Model 2	
Leukaemia				
A and B	0.112	6900.5	6899.942	A
B and C	0.428	6899.9	6901.32	
B and D	0.503	6899.9	6901.33	
Lymphoma				
A and B	<0.001	11930	11887.95	B
B and C	0.819	11888	11889.90	
B and D	0.574	11888	11890.32	
CNS Tumours				
A and B	<0.001	8901.00	8882.79	B
B and C	0.676	8882.79	8884.61	
B and D	0.168	8882.79	8887.68	

Higher levels of population mixing associated with a reduced risk of CNS tumours may have occurred through a protective effect for exposure to infection, since population mixing has been shown to be a reasonable proxy for infectious exposure [36]. One possible mechanism may involve immune system priming in early life by exposure to a wide range and high volume of infection, and may be important in terms of protection against later development of CNS tumours among TYAs.

Our interest in assessing whether there was any relationship between population mixing and the incidence of TYA cancer was motivated through increasing evidence that infections may play a role in the development of certain childhood cancers such as leukaemia [8,37], lymphoma and CNS tumours [38], the latter specifically giving evidence of space-time clustering for astrocytoma in older children. Only one specific infectious agent, the polyomavirus, has been implicated in the disease aetiology for CNS tumours [39]. Besides associations with population mixing and deprivation, we have also shown that certain CNS tumours exhibit seasonality around the time of birth (with peaks in May and November for glioma) and diagnosis (peaks in December and June) [25].

Strengths and limitations

This was the first national population-based study to evaluate the risk of TYA cancer in relation to population mixing, adjusting for the potentially confounding effects of deprivation and population density. As previously stated, use of population mixing has been shown to be a reliable proxy measure for infection in ecological study designs [36].

Our study design was an aggregation of individual counts of cancer occurring at ward level, thus the reported associations may be subject to the ecological fallacy [40]. Nevertheless, census wards are small, with a 15–24 year old population of around 900 people per ward on average. Furthermore, wards have been shown to have relatively homogeneous population sizes when compared to larger geographical areas such as district level [11], in our case the 15–24 year old population ranged in size from 126 to 4015 per ward for 98% of wards. In addition we were able to link all cases in the study to a census ward thus avoiding any selection bias. We chose to allocate levels of population mixing, deprivation and population density based on matching cases to the 1991 census. Although relative levels of population mixing do not change markedly from one census to the next (Dr Zhiqiang Feng, personal communication), this could have led to measurement error with cases born between 1971 and 1990 and diagnosed between 1996 and 2005, with the possibility that cases may have moved residence several times between birth and

diagnosis. Nor were we able to distinguish whether time since exposure or age at exposure may have been of greater importance given the age range and period of diagnosis of subjects included in the analysis. The key timing window of exposure to levels of mixing in relation to the risk of cancer in TYAs is uncertain, particularly for CNS tumours which comprise a number of different benign tumours with long latency periods and potentially distinct aetiologies.

Conclusion

In summary, there is an emerging epidemiological picture implicating an environmental aetiology for TYA cancers, especially for certain CNS tumours, and future work examining correlates of population mixing and deprivation would be worthwhile. This could be achieved by undertaking a more comprehensive and focused geographical analysis, for example by identifying specific areas or regions, which exhibit significantly elevated incidence for CNS tumours and correlating these to levels of circulating infection in the community over several decades. Individual residential and exposure histories documenting infectious episodes would be valuable to discern the association between infection and the risk of TYA cancers. This could be achieved by linking primary and secondary care data to national cancer registration data to evaluate consultations and admissions related to infection.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MvL carried out the data cleaning, statistical analysis and drafted the manuscript. SEK and SVP participated in the design and helped draft the manuscript. DPS, PM and RCP provided input into the analysis and design of the study and participated in critically revising the manuscript by providing important intellectual content. RGF conceived the study, participated in the design and coordination of the study, helped with the statistical analysis and to draft the manuscript. All authors read and approved the final manuscript.

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